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(54) Title: ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE

(57) Abstract

Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues.

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ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE

Background of the Invention

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

The use of quinolone antibiotics to treat infections represents the current state of the art in the field of ophthalmic pharmaceutical compositions and methods of treatment. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

Quinolone	Product	Manufacturer
Ofloxacin	OCUFLOX™	Allergan
Norfloxacin	CHIBROXIN™	Merck
Lomefloxacin	LOMEFLOX™	Senju

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic, otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

Summary of the Invention

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the prophylactic use of these antibiotics following surgery or other trauma to ophthalmic, otic or nasal tissues. The compositions

of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgery procedures to prevent or alleviate post-surgical infections.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

Examples of otic conditions that may be treated with the compostions of the present invention include otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

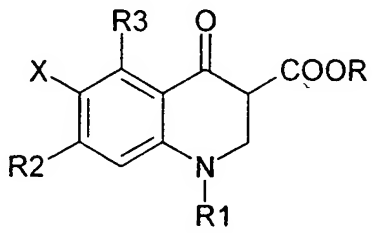
The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for

application to ophthalmic, otic and nasal tissues, including tissues that have been compromised

Detailed Description of the Invention

The antibiotics used in the compositions and methods of the present invention have the following formula:

(I)



wherein

R1 is a cyclopropyl which may be substituted by 1 to 3 of substituents selected from the group consisting of a C_1-C_6 alkyl and a halogen atom, a phenyl which may be substituted by 1 to 3 of substituents selected from the group consisting of C_1-C_6 alkoxy, a halogen atom and hydroxy, a C_1-C_6 alkyl which may be substituted by a halogen atom, a C_2-C_6 alkanoyloxy or hydroxy, a C_2-C_6 alkenyl or thienyl;

R2 is a member selected from the group consisting of a 1-piperazinyl group which may have 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkanoyl group, a phenyl (C_1-C_6) alkyl group, and a 2-oxo-1,3-dioxolenemethyl group which may be substituted by a phenyl group or a C_1-C_6 alkyl group; a 1-pyrrolidinyl group which may have 1 to 3 substituents selected

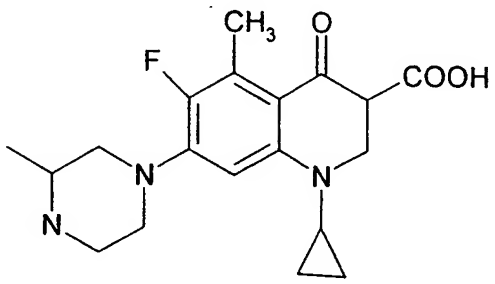
from the group consisting of an amino group which can have 1 or 2 substituents selected from a C_1-C_6 alkyl group and a (C_1-C_6)alkooxy-carbonyl group, an amino(C_1-C_6)alkyl group which may have 1 to 2 substituents selected from C_1-C_6 alkyl group and a (C_1-C_6)alkoxy-carbonyl group on the amino moiety, and a C_1-C_6 alkyl group; a morpholino group which may have 1 to 3 substituents of C_1-C_6 alkyl groups; a 1-piperidinyl group which may have 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, hydroxy, a halogen atom and oxo group; and a 1,4-diazobicyclo[4.3.0]nonan-4-yl group;

R3 is a C_1-C_6 alkyl;

R is hydrogen atom or a C_1-C_6 alkyl; and

X is a halogen atom, or a pharmaceutically acceptable salt thereof.

The compound Grepafloxacin is most preferred. Grepafloxacin has the following structure:



Further details regarding the structure, preparation, and physical properties of Grepafloxacin and other compounds of formula (I) are provided in U. S. Patent No. 5,563,138.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC". The term "MIC90" refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Grepafloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:

Microorganism	MIC_{90}
S. aureus/methicillin sensitive	0.13
S. aureus/methicillin resistant	0.13
S. aureus/quinolone resistant	0.13
S. epidermidis/methicillin sensitive	0.13
S. epidermidis/methicillin resistant	0.13
S. pneumoniae/penicillin sensitive	0.25
S. pneumoniae/penicillin resistant	0.25
P. aeruginosa	8.0
H. influenzae/β-lactamase positive	0.008
H influenzae/βlactamase negative	0.008

All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

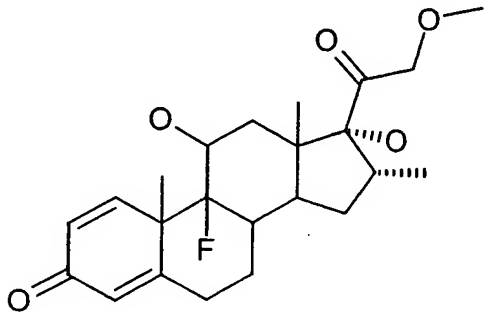
The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than

the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as "an antimicrobial effective amount". The compositions of the present invention will typically contain one or more compounds of formula (I) in a concentration of from about 0.1 to about 1.0 percent by weight ("wt. %") of the compositions.

The compositions of the present invention may also contain one or more anti-inflammatory agents. The anti-inflammatory agents utilized in the present invention are broadly classified as steroidal or non-steroidal. The preferred steroidal anti-inflammatory agents are glucocorticoids.

The preferred glucocorticoids for ophthalmic and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

The dexamethasone derivatives described in U.S. Patent No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating ophthalmic inflammation. The following compounds are especially preferred:



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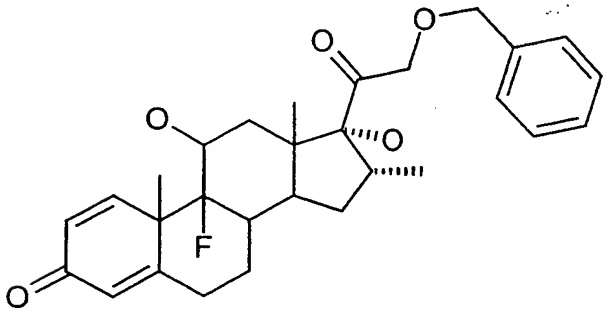


AL-2512

These compounds are referred to herein as "21-ether derivatives of dexamethasone". The 21-benzyl ether derivative (i.e., compound AL-2512) is particularly preferred.

The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthetase inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016,

HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib; P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein as "an anti-inflammatory effective amount". The compositions of the present invention will typically containe one or more anti-inflammatory agents in an amount of from about 0.01 to about 1.0 wt.%.

The compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition, one to four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected ophthalmic, otic or nasal tissues during surgical procedures.

The ophthalmic, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one or more anti-inflammatory agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The ophthalmic compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and

ophthalmic tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram of water ("mOsm/kg"), but will preferably be about 300 mOsm/kg.

Ophthalmic, otic and nasal products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase absorption of the active compounds by the target tissues or increase the retention time in the eye, ear or nose. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The following examples are provided to further illustrate the ophthalmic, otic and nasal compositions of the present invention.

Example 1

Ophthalmic/Otic/Nasal Solution

Ingredient	Amount (wt. %)
Grepafloxacin	0.35
Sodium Acetate	0.03
Acetic Acid	0.04
Mannitol	4.60
EDTA	0.05
Benzalkonium Chloride	0.006
Water	q.s. 100

Example 2

Ophthalmic/Otic/Nasal Suspension

Ingredient	Amount (wt. %)
Grepafloxacin	0.3
Dexamethasone, Micronized USP	0.10
Benzalkonium Chloride	0.01
Edetate Disodium, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or	
Sodium Hydroxide, NF	q.s. for pH adjustment to 5.5
Purified Water, USP	q.s. to 100

Example 3

Ophthalmic Ointment

Ingredient	Amount (wt.%)
Grepafloxacin	0.35
Mineral Oil, USP	2.0
White petrolatium, USP	q.s 100

Example 4

Ophthalmic Ointment

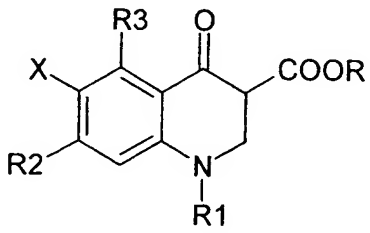
Ingredient	Amount (wt.%)
Grepafloxacin	0.3
Fluorometholone Acetate, USP	0.1
Chlorobutanol, Anhydrous, NF	0.5
Mineral Oil,USP	5
White Petrolatum, USP	q.s. 100

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

What is claimed is:

1. A topical ophthalmic, otic or nasal pharmaceutical composition comprising an antimicrobial effective amount of one or more compounds of the formula:

(I)



wherein

R1 is a cyclopropyl which may be substituted by 1 to 3 of substituents selected from the group consisting of a C_1-C_6 alkyl and a halogen atom; a phenyl which may be substituted by 1 to 3 of substituents selected from the group consisting of C_1-C_6 alkoxy, a halogen atom and hydroxy; a C_1-C_6 alkyl which may be substituted by a halogen atom, a C_2-C_6 alkanoyloxy or hydroxy; a C_2-C_6 alkenyl; or thienyl;

R2 is a member selected from the group consisting of a 1-piperazinyl group which may have 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkanoyl group, a phenyl (C_1-C_6) alkyl group, and a 2-oxo-1,3-dioxolenemethyl group which may be substituted by a phenyl group or a C_1-C_6 alkyl group; a 1-pyrrolidinyl group which may have 1 to 3 substituents selected from the group consisting of an amino group which can have 1 or 2 substituents selected from a C_1-C_6 alkyl group and a (C_1-C_6)alkooxy-carbonyl group, an

amino(C_1-C_6)alkyl group which may have 1 to 2 substituents selected from C_1-C_6 alkyl group and a (C_1-C_6)alkoxy-carbonyl group on the amino moiety, and a C_1-C_6 alkyl group; a morpholino group which may have 1 to 3 substituents C_1-C_6 alkyl groups; a 1-piperidinyl group which may have 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, hydroxy, a halogen atom and oxo group; and a 1,4-diazobicyclo[4.3.0]nonan-4-yl group;

R3 is a C_1-C_6 alkyl;

R is hydrogen atom or a C_1-C_6 alkyl; and

X is a halogen atom, or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable vehicle therefor.

2. A topical composition according to Claim 1, wherein the composition further comprises an anti-inflammatory effective amount of a steroidal or non-steroidal anti-inflammatory agent.

3. A topical composition according to Claim 2, wherein the anti-inflammatory agent comprises a glucocorticoid.

4. A topical composition according to Claim 3, wherein the glucocorticoid is selected from the group consisting of dexamethasone, rimexolone, prednisolone, fluorometholone, hydrocortisone, mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

5. A topical composition according to Claim 2, wherein the anti-inflammatory agent comprises a non-steroidal agent selected from the group consisting of prostaglandin H synthetase inhibitors, PAF antagonists, and PDE IV inhibitors.

6. A topical composition according to Claim 1, wherein the compound of formula (I) comprises grepafloxacin.

7. A topical composition according to Claim 6, wherein the composition further comprises an anti-inflammatory effective amount of a steroidal or non-steroidal anti-inflammatory agent.

8. A method of treating or preventing ophthalmic, otic or nasal infections, which comprises topically applying a therapeutically effective amount of the composition of Claim 1 to the affected ophthalmic, otic or nasal tissue.

9. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 2 to the affected ophthalmic, otic or nasal tissue.

10. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 7 to the affected ophthalmic, otic or nasal tissue.

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/US 99/22625

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4725 A61K31/5377 A61K31/496 A61K31/573 A61P11/02 A61P7/02 A61P27/16 A61P31/04 //(A61K31/573,31:4725), (A61K31/573,31:5377),(A61K31/573,31:496)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 563 138 A (UEDA HIRAKI ET AL) 8 October 1996 (1996-10-08) cited in the application column 40, line 7-18; claims 1,21 ---	1-10
Y	"New Antimicrobial Agents Approved by the U.S Food and Drug Administration in 1997 and New Indications for Previously Approved Agents" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 42, no. 4, - 1 April 1998 (1998-04-01) pages 987-988, XP000872060 USA page 988, line 29-33 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	14/02/2000

Name and mailing address of the ISA	Authorized officer
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Int. ional Application No
PCT/US 99/22625

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 39146 A (BAYER AG) 12 December 1996 (1996-12-12) claims 1-10	1-10
Y	WO 90 01933 A (ALCON LAB INC) 8 March 1990 (1990-03-08) claim 1	1-10
Y	US 4 551 456 A (KATZ IRVING M) 5 November 1985 (1985-11-05) claim 1	1-10
Y	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 10, 31 August 1998 (1998-08-31) & JP 10 130148 A (SENJU PHARMACEUT CO LTD), 19 May 1998 (1998-05-19) abstract	1-10
Y	PATENT ABSTRACTS OF JAPAN vol. 012, no. 472 (C-551), 9 December 1988 (1988-12-09) & JP 63 190826 A (DAI ICHI SEIYAKU CO LTD;OTHERS: 01), 8 August 1988 (1988-08-08) abstract	1-10

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Information on patent family members

Inte onal Application No
PCT/US 99/22625

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